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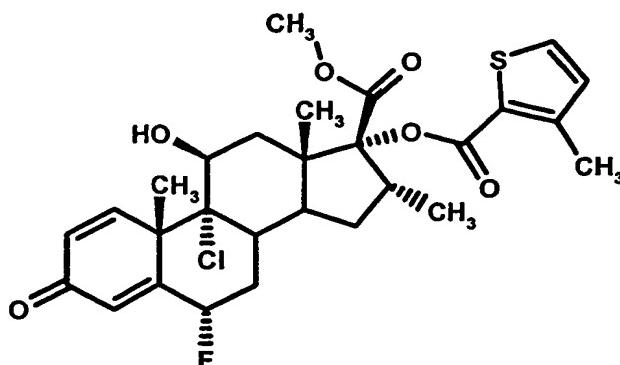
WO 2004/013156 A1

(54) Title: POLYMORPHIS OF A KNOWN THIOPHENECARBOXYLIC ACID DODECAHYDROCYCLOPENTA (A) PHENANTHRENYL ESTER

(57) Abstract: Polymorphic crystal forms of 3-methylthiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester. The crystal forms possess anti-inflammatory activity and have very good stability. Methods for preparing the crystal forms are also described.

POLYMORPHIS OF A KNOWN THIOPHENECARBOXYLIC ACID DODECAHYDROCYCLOPENTA (A) PHENANTHRENYL ESTER

This invention relates to new polymorphic crystal forms of a compound of formula I and methods for preparing them.

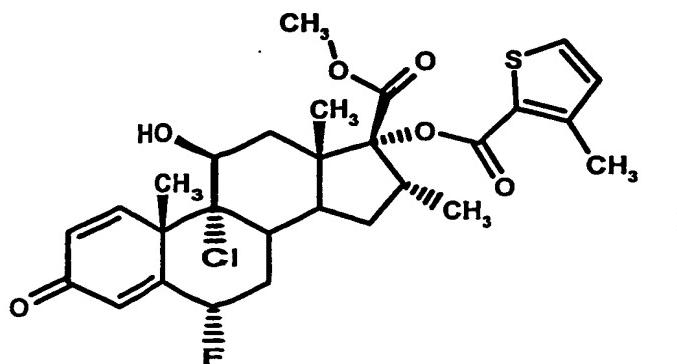


The compound of formula I, namely 3-methylthiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl ester, possesses a high anti-inflammatory activity. This activity can be demonstrated by its inhibition of TNF-alpha synthesis and release in a human macrophage cell line and by its inhibition of inflammatory conditions, particularly in the airways, e.g. inhibition of eosinophil activation, in animal models, e.g. mouse or rat models of airways inflammation, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin. Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

This compound has been investigated for use as a pharmaceutical. The existence of various crystallisation polymorphic forms of the compound has been explored in order to determine the most appropriate form of the compound for the proposed use.

Novel crystal forms of the compound of formula I have now been isolated. Some of these novel crystal forms have very good stability, facilitating their use in the preparation of pharmaceutical dosage forms.

Accordingly, the present invention provides in one aspect a compound of formula I



in a crystal form A that has a melting point, by Differential Scanning Calorimetry, of about 264°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 3.6°, 7.3°, 13.4°, 14.6°, 18.3°, 22.0°, 25.8°, 25.9°, 29.5°; or

in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

Crystal form A may be prepared by crystallising the compound of formula I from a solution thereof in an organic solvent such as isopropanol, ethyl acetate, n-butanol, hexane, heptane, tert-butylmethylether, toluene or tetrahydrofuran, for example by equilibrating the compound in that solvent over 24 hours at 25° C, or analogously such as hereinafter described in Example 1. The crystallisation may be induced by, for example, cooling a supersaturated solution of the compound of formula I in the solvent, or by adding to the solution of the compound of formula I a solvent in which the compound of formula I is less soluble. The starting solution of the compound of formula I may be at ambient or elevated (up to reflux) temperature.

Crystal form B may be prepared by crystallising the compound of formula I from a solution thereof in a polar organic solvent such as ethanol, methanol or methylene chloride, for example by equilibrating the compound in that solvent over 24 hours at 25° C, or analogously such as hereinafter described in Example 2. The crystallisation may be induced by, for example, cooling a supersaturated solution of the compound of formula I in the polar solvent,

or by adding to the solution of the compound of formula I a polar solvent in which the compound of formula I is less soluble. The starting solution of the compound of formula I may be at ambient or elevated (up to reflux) temperature.

For the preparation of each of the crystal forms, working up may be carried out generally using known procedures for the separation of the crystallise from the mother liquor, for example by filtration, with or without the assistance of pressure and/or vacuum, or by centrifugation, and subsequent drying of the crystallise.

In the presence of ethanol crystal form A converts to crystal form B. In the presence of isopropanol crystal form B converts to crystal form A.

The crystal forms can be distinguished in particular by their X-ray powder diagrams. X-ray diagrams taken with a diffractometer and using Cu-K α_1 -radiation are preferably used to characterise solids of organic compounds. X-ray powder diffraction diagrams are particularly useful to determine the crystal form or modification of the compound of formula I. The use of such diagrams is described in the accompanying Examples.

Crystal form A appears to be more thermodynamically stable than crystal form B in the solid state. However, in suspension with solvents the stability is solvent dependent.

The compound of formula I may be prepared in accordance with the method given in Example 26 of international patent application WO 02/00679.

Given its anti-inflammatory activity, the compound of formula I in crystal form A or B is useful in the treatment of inflammatory conditions, particularly inflammatory or obstructive airways diseases. Treatment in accordance with the invention may be symptomatic or prophylactic.

Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern

and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".) Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to its anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, the compound of formula I in crystal form A or B is also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-

Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

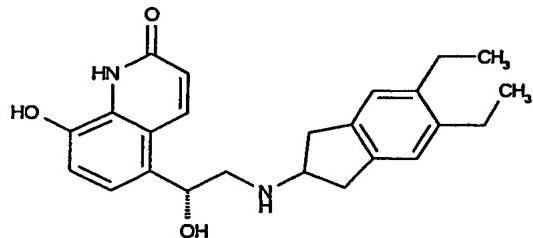
The compound of formula I in crystal form A or B is also useful in the treatment of inflammatory conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisis, epidermolysis bullosa acquisita, and other inflammatory conditions of the skin. The compound of formula I in crystal form A or B may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, diseases of the joints such as rheumatoid arthritis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease.

The compound of formula I in crystal form A or B is also useful as a co-therapeutic agent for use in conjunction with other drug substances for treatment of airways diseases, particularly bronchodilatory or anti-inflammatory drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned herein before, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. The compound of formula I in crystal form A or B may be mixed with the other drug in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug.

Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate and compounds described in WO 0200679, WO 0288167, WO 0212266 and WO 02100879; LTB4 antagonists such as those described in US 5451700; LTB4 antagonists such as those described in US 5451700; LTD4 antagonists such as montelukast and zafirlukast; dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)-propyl]sulfonyl]ethyl]amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca); PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo); A2a agonists such as those described in EP 1052264,

EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774; and A2b antagonists such as those described in WO 02/42298.

Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, such as those described in EP 424021, US 5171744 (Pfizer) and WO 01/04118 (Almirall Prodesfarma) and but in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, and beta-2 adrenoceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International Publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



in free or pharmaceutically acceptable salt or solvate form.

Combinations of the compound of formula I in crystal form A or B and beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma.

Combinations of the compound of formula I in crystal form A or B and anticholinergic or antimuscarinic agents, PDE4 inhibitors, LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the invention also provides a method for the treatment of an inflammatory condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof an effective amount of the compound of formula I in crystal form A or B as hereinbefore described. In another aspect the invention provides the use of the compound of formula I in crystal form A or B for the manufacture of a medicament for the treatment of an inflammatory condition, particularly an inflammatory or obstructive airways disease.

The compound of formula I in crystal form A or B may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of inflammatory or obstructive airways disease; intranasally, for example in the treatment of allergic rhinitis; topically to the skin, for example in the treatment of atopic dermatitis; or rectally, for example in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient the compound of formula I in crystal form A or B optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent such as a bronchodilatory or anti-inflammatory drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I in crystal form A or B having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I in crystal form A or B either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

The invention includes (A) the compound of formula I in crystal form A or B in inhalable form, e.g. in an aerosol or other atomisable composition or in inhalable particulate, e.g. micronised, form, (B) an inhalable medicament comprising the compound of formula I in crystal form A or B in inhalable form; (C) a pharmaceutical product comprising the compound of formula I in crystal form A or B in inhalable form in association with an inhalation device;

and (D) an inhalation device containing the compound of formula I in crystal form A or B in inhalable form.

Dosages of the compound of formula I in crystal form A or B employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005 to 10 mg, while for oral administration suitable daily doses are of the order of 0.05 to 100 mg.

The invention is illustrated by the following Examples.

Example 1

Preparation and characterisation of Crystal Form A

50 mg of the compound of formula I is equilibrated in 1 ml isopropanol over 24 hours at 25 °C. The product is filtered and dried. After drying the compound of formula I is obtained in the form of white crystals.

Measurements are made by X-ray powder diffraction and using Cu-K α_1 . The X-ray diffraction pattern thus determined, as represented by the reflection lines and intensities of the most important lines, is shown in Figure 1 and characterised in Table 1 below.

TABLE 1
X-ray diffraction lines and intensities for crystal form A

2θ	Intensity
3.6	medium
7.3	strong
13.4	medium
14.6	strong
18.3	medium
22.0	medium
25.8	strong
25.9	medium
29.5	medium

Example 2**Preparation and characterisation of Crystal Form B**

87 mg of the compound of formula I are equilibrated in 2 ml ethanol over 24 hours at 25 °C. The product is filtered and dried. After drying the compound of formula I is obtained in the form of white crystals.

Measurements are made by X-ray powder diffraction and using Cu-K α_1 . The X-ray diffraction pattern thus determined, as represented by the reflection lines and intensities of the most important lines, is shown in Figure 2 and characterised in Table 2 below.

TABLE 2
X-ray diffraction lines and intensities for crystal form B

2θ	Intensity
7.2	strong
9.3	Medium
12.0	Medium
12.8	Medium
13.1	Medium
14.5	Strong
17.4	Medium
20.4	Medium
23.2	Medium
25.8	Medium

Example 3**Preparation of Crystal forms A and B in various solvents**

8 mg of the compound of formula I are equilibrated with 1.5 ml of a variety of solvents for at least 24 hours in a water bath at 25°C ± 0.1. The solutions are filtered and dried for 10 minutes in the air. The solid part is investigated by X-ray powder diffraction (XRPD) to identify the crystal form produced. The results are shown in Table 3 below.

The procedure is repeated at 50°C ± 0.1 and 70°C ± 0.1 and the results are shown in Tables 4 and 5 respectively.

TABLE 3
Equilibration with solvent at 25°C

Solvent	XRPD
n-Butanol	Crystal form A
Ethanol	Crystal form B
Ethyl acetate	Crystal form A
Isopropanol	Crystal form A
Hexane	Crystal form A
Heptane	Crystal form A
Methanol	Crystal form B
Methylene chloride	Crystal form B
Tert-butylmethylether	Crystal form A
Toluene	Crystal form A
Tetrahydrofuran	Crystal form A
Water	Crystal forms A + B

TABLE 4
Equilibration with solvent at 50°C

Solvent	XRPD
n-Butanol	Crystal form A
Ethanol	Crystal form B
Ethyl acetate	Crystal form A
Isopropanol	Crystal form A
Hexane	Crystal form A
Heptane	Crystal form A
Methanol	Crystal form B
Methylene chloride	Crystal form B
Tert-butylmethylether	Crystal form A
Tetrahydrofuran	Crystal form A
Toluene	Crystal form A
Water	Crystal forms A + B

TABLE 5
Equilibration with solvent at 70°C

Solvent	XRPD
n-Butanol	Crystal form A
Ethanol	Crystal form B
Isopropanol	Crystal form A

These results show that the choice of solvent dictates which crystal form of the compound of formula I is formed.

Example 4**Stability of Crystal Forms A and B**

Samples of the compound of formula I in crystal form A, the compound of formula I in crystal form B, a mixture of both crystal forms and an amorphous form of the compound of formula I (obtained by spray drying) are stored for 4 weeks at 80° C under different conditions and analyzed by X-ray powder diffraction (XRPD). The results are shown in Table 6 below.

TABLE 6: Stability after 4 weeks at 80°C

Conditions	Sealed	75% r.h.* open	N ₂	N ₂ + 2% water	O ₂
Crystal form A	A	A	A	A	A
Crystal form B	B	A+B	B	A+B	A+B
Crystal forms A + B	A+B	A+B	A+B	A+B	A+B
Amorphous form	A	A	A	A	A

* relative humidity

These results show that crystal form B can convert at least partially in the solid state into crystal form A when stored for 4 weeks at 80°C. The amorphous form can also convert into crystal form A. This suggests crystal form A is more thermodynamically stable than crystal form B.

Example 5**Heat of solution experiments**

The heat of solution of samples of crystal forms A and B of the compound of formula I are measured at 25°C in acetone. The results are shown in Table 7 below.

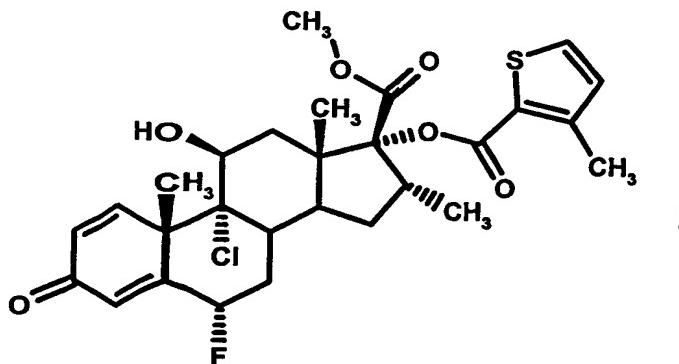
TABLE 7: Heat of solution at 25°C in acetone

Crystal form	Heat of solution (J/g)
A	29.3
B	17.9

These results show crystal form A has a higher endothermic heat of solution compared with crystal form B. This indicates crystal form A is more thermodynamically stable than crystal form B.

CLAIMS

1. A compound of formula I



in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

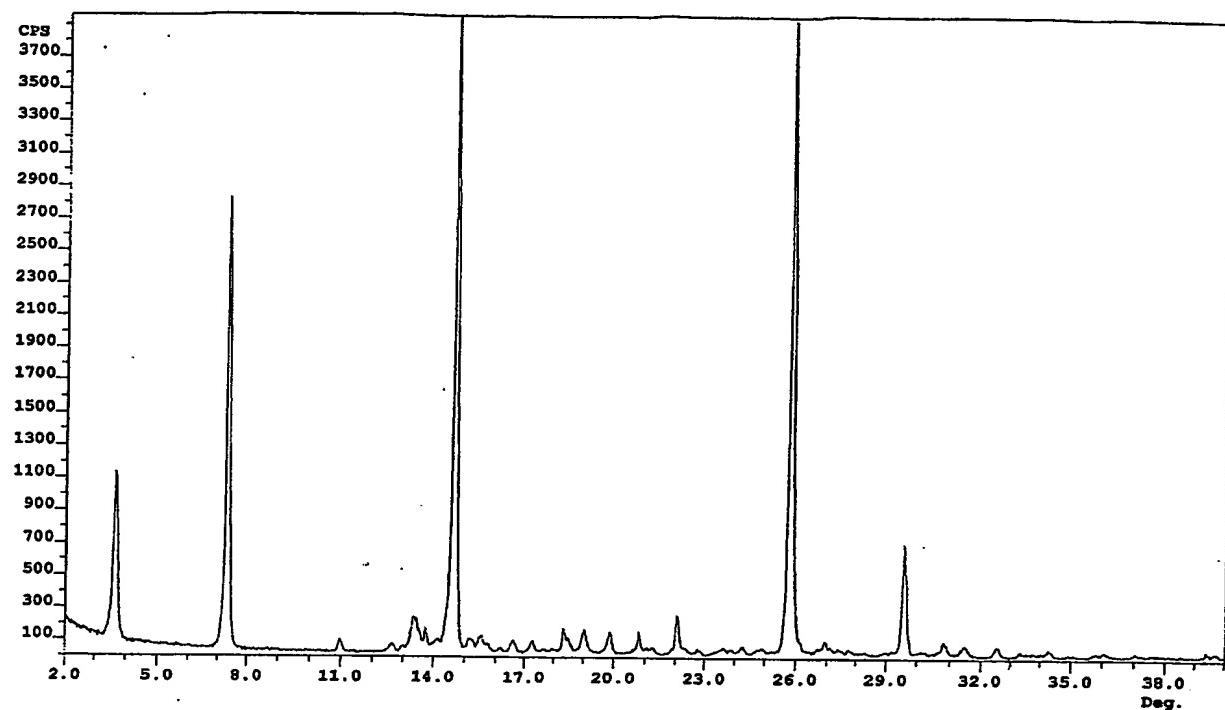
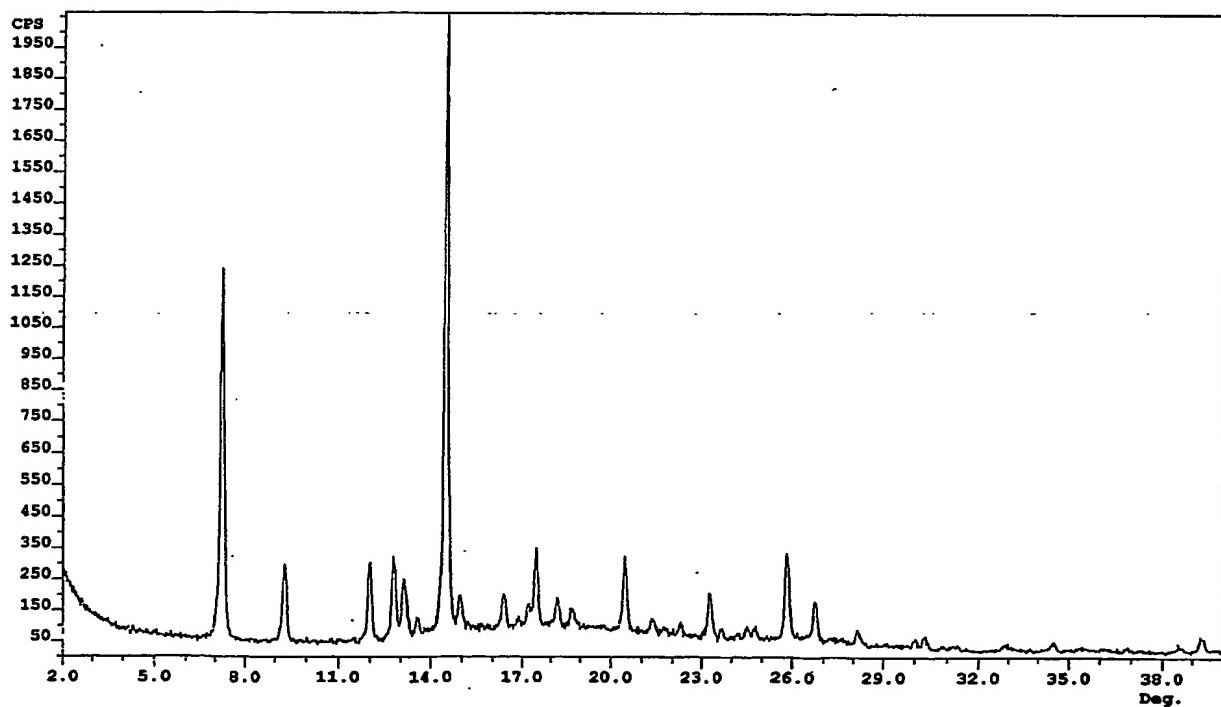
2. A pharmaceutical composition comprising, as active ingredient, an effective amount of the compound of formula I in crystal form A or B as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

3. A composition according to claim 2, which is in inhalable form.

4. The use of a compound according to claim 1 in crystal form A or B for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

5. A method of preparing a compound of formula I in crystal form A as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in isopropanol, ethyl acetate, n-butanol, hexane, heptane, tert-butylmethylether, toluene or tetrahydrofuran.

6. A method of preparing a compound of formula I in crystal form B as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in ethanol, methanol or methylene chloride.
7. A crystal form of the compound of formula I, substantially as herein described with reference to any of the Examples.
8. A crystal form of the compound of formula I, substantially as herein described with reference to either of the drawings.

FIG 1**FIG 2**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08314

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J33/00 A61K31/58 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	<p>WO 02 00679 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG (CH); BEATTIE DAVID (GB)) 3 January 2002 (2002-01-03) cited in the application Abstract; page 26, last paragraph; claims 12,13; page 12, paragraphs 2 and 3. ---</p>	1-6
Y	<p>HALEBLIAN J ET AL: "PHARMACEUTICAL APPLICATIONS OF POLYMORPHISM" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 58, no. 8, 1 August 1969 (1969-08-01), pages 911-929, XP002020518 ISSN: 0022-3549 the whole document -----</p>	1-6

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

11 November 2003

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Weisbrod, T

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-8

The vague phrase "substantially as herein described" used in claims 7 and 8 is so unclear (Article 6 PCT) that a meaningful search is impossible for these claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08314

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 7-8 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP 03/08314

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